protein level and preventing the decline of renal function in membranous nephropathy showing a non-nephrotic range of proteinuria?

1. Hladunewich MA, et al. Clin J Am Soc Nephrol 2009 ; 4 : 1417–22. (Level 4)

3) Membranoproliferative glomerulonephritis

CQ 13. Is steroid treatment recommended for reducing urinary protein level and preventing the decline of renal function in idiopathic membranoproliferative glomerulonephritis showing nephrotic syndrome?

1. Tarshish P, et al. Pediatr Nephrol 1992 ; 6 : 123–30. (Level 2)
2. McEnery PT. J Pediatr 1990 ; 116 : S109–14. (Level 4)
3. Warady BA, et al. J Pediatr 1985 ; 107 : 702–7. (Level 4)
4. Emre S, et al. Acta Paediatr Jpn 1995 ; 37 : 626–9. (Level 4)
5. Bergstein JM, et al. Pediatr Nephrol 1995 ; 9 : 268–71. (Level 4)
6. Ford DM, et al. Kidney Int 1992 ; 41 : 1606–12. (Level 4)
7. Donadio JV Jr, et al. Am J Kidney Dis 1989 ; 14 : 445–51. (Level 5)

4) Steroid treatment

CQ 14. Is oral steroid treatment recommended during intervals between steroid pulse treatments (i.e., at days when no steroid pulse treatment is given)?

CQ 15. Is the increase of oral steroid doses or the change of administration routes recommended for patients with systemic edema?

1. Frey FJ, et al. Am J Kidney Dis 1984 ; 3 : 339–48. (Level 4)
2. Bergrem H. Kidney Int 1983 ; 23 : 876–81. (Level 4)

CQ 16. Is alternate-day administration as a means of steroid dose reduction effective for inhibiting the incidence of adverse effects?

1. Mak SK, et al. Nephrol Dial Transplant 1996 ; 11 : 2192–201. (Level 4)
2. Waldman M, et al. Clin J Am Soc Nephrol 2007 ; 2 : 445–53. (Level 4)
3. Carter ME, et al. Ann Rheum Dis 1972 ; 31 : 379–83. (Level 4)
4. Kimura Y, et al. J Rheumatol 2000 ; 27 : 2018–24. (Level 4)
5. Byron MA, et al. J R Soc Med 1983 ; 76 : 452–7. (Level 4)

CQ 17. Is reducing the steroid dose compared with that of the first treatment recommended for the treatment of recurrent nephrotic syndrome?

1. Fujimoto S, et al. Am J Kidney Dis 1991 ; 17 : 687–92. (Level 4)
2. Nakayama M, et al. Am J Kidney Dis 2002 ; 39 : 503–12. (Level 4)
3. Takei T, et al. Clin Exp Nephrol 2007 ; 11 : 214–7. (Level 4)
4. Imbasciati E, et al. Br Med J 1985 ; 291 : 1305–8. (Level 2)

CQ 18. Is there a standard period for steroid maintenance therapy after nephrotic syndrome has remitted?

1. Huang JJ, et al. Am J Nephrol 2001 ; 21 : 28–34. (Level 4)
2. Mak SK, et al. Nephrol Dial Transplant 1996 ; 11 : 2192–201. (Level 4)
3. Waldman M, et al. Clin J Am Soc Nephrol 2007 ; 2 : 445–53. (Level 4)
4. Korbet SM, et al. Am J Kidney Dis 1994 ; 23 : 773–83. (Level 2)
5. Banfi G, et al. Clin Nephrol 1991 ; 36 : 53–9. (Level 4)
6. Cattran DC, et al. Am J Kidney Dis 1998 ; 32 : 72–9. (Level 4)
7. Rydel JJ, et al. Am J Kidney Dis 1995 ; 25 : 534–42. (Level 4)
8. Tarshish P, et al. Pediatr Nephrol 1992 ; 6 : 123–30. (Level 2)
9. McEnery PT. J Pediatr 1990 ; 116 : S109–14. (Level 4)
10. Warady BA, et al. J Pediatr 1985 ; 107 : 702–7. (Level 4)
11. Bergstein JM, et al. Pediatr Nephrol 1995 ; 9 : 268–71. (Level 4)

5) Immunosuppressive agents not allowed by medical insurance (at the time of description of this guideline in 2013)

CQ 19. Is rituximab recommended for reducing urinary protein level and preventing the decline of renal function in nephrotic syndrome?

1. Sugiura H, et al. Nephron Clin Pract 2011 ; 117 : c98–105. (Level 5)
2. Fernandez–Fresnedo G, et al. Clin J Am Soc Nephrol 2009 ; 4 : 1317–23. (Level 4)
3. Ravani P, et al. Clin J Am Soc Nephrol 2011 ; 6 : 1308–15. (Level 2)
4. Bomback AS, et al. Clin J Am Soc Nephrol 2009 ; 4 : 734–44. (Level 5)
5. Segarra A, et al. Clin J Am Soc Nephrol 2009 ; 4 : 1083–8. (Level 5)
6. Fervenza FC, et al. Clin J Am Soc Nephrol 2010 ; 5 : 2188–98. (Level 5)

CQ 20. Is mycophenolate mofetil recommended for reducing urinary protein level and preventing the decline of renal function in nephrotic syndrome?

1. Lee YH, et al. Lupus 2010 ; 19 : 703–10. (Level 2)
2. Zhu B, et al. Nephrol Dial Transplant 2007 ; 22 : 1933–42. (Level 1)

3. Dorresteijn EM, et al. Pediatr Nephrol 2008 ; 23 : 2013–20. (Level 2)
4. Ito S, et al. Pediatr Nephrol 2011 ; 26 : 1823–8. (Level 3)
5. Senthil Nayagam L, et al. Nephrol Dial Transplant 2008 ; 23 : 1926–30. (Level 2)
6. Dussol B, et al. Am J Kidney Dis 2008 ; 52 : 699–705. (Level 2)
7. Branten AJ, et al. Am J Kidney Dis 2007 ; 50 : 248–56. (Level 3)
8. Chan TM, et al. Nephrology (Carlton) 2007 ; 12 : 576–81. (Level 2)

CQ 21. Is azathioprine recommended for reducing urinary protein level and preventing the decline of renal function in nephrotic syndrome?

1. Sharpstone P, et al. Br Med J 1969 ; 2 : 535–9. (Level 2)
2. Cade R, et al. Arch Intern Med 1986 ; 146 : 737–41. (Level 4)
3. Hiraoka M, et al. Pediatr Nephrol 2000 ; 14 : 776–8. (Level 5)
4. Goumenos DS, et al. Nephron Clin Pract 2006 ; 104 : c75–82. (Level 4)
5. Abramowicz M, et al. Lancet 1970 ; (1 7654) : 959–61. (Level 2)
6. Adeniyi A, et al. Arch Dis Child 1979 ; 54 : 204–7. (Level 2)
7. Habashy D, et al. Pediatr Nephrol 2003 ; 18 : 906–12. (Level 2)
8. Colquitt JL, et al. Health Technol Assess 2007 ; 11 : iii–iv, ix–xi, 1–93. (Level 2)
9. Western Canadian Glomerulonephritis Study Group, et al. Can Med Assoc J 1976 ; 115 : 1209–10. (Level 2)
10. Ahuja M, et al. Am J Kidney Dis 1999 ; 34 : 521–9. (Level 2)
11. Goumenos DS, et al. Clin Nephrol 2006 ; 65 : 317–23. (Level 3)
12. Brown JH, et al. Nephrol Dial Transplant 1998 ; 13 : 443–8. (Level 4)
13. Williams PS, et al. Nephrol Dial Transplant 1989 ; 4 : 181–6. (Level 4)
14. Naumovic R, et al. Biomed Pharmacother 2011 ; 65 : 105–10. (Level 2)

6) Nephrotic syndrome in the elderly

CQ 22. Are immunosuppressive agents recommended for elderly patients with nephrotic syndrome?

1. Deegens JK, et al. Drugs Aging 2007 ; 24 : 717–32. (Level 5)
2. Passerini P, et al. Nephrol Dial Transplant 1993 ; 8 : 1321–5. (Level 3)
3. Bizzarri D, et al. Contrib Nephrol 1993 ; 105 : 65–70. (Level 5)
4. Nolasco F, et al. Kidney Int 1986 ; 29 : 1215–23.
5. Tse KC, et al. Nephrol Dial Transplant 2003 ; 18 : 1316–20. (Level 4)
6. Al–Khader AA, et al. Clin Nephrol 1979 ; 11 : 26–30. (Level 4)
7. Nagai R, et al. Clin Nephrol 1994 ; 42 : 18–21. (Level 4)
8. Zent R, et al. Am J Kidney Dis 1997 ; 29 : 200–6. (Level 4)
9. Branten AJ, et al. QJM 1998 ; 91 : 359–66. (Level 4)
10. Ponticelli C, et al. J Am Soc Nephrol 1998 ; 9 : 444–50. (Level 2)
11. Quaglia M, et al. Drugs 2009 ; 69 : 1303–17. (Level 5)

7) Adjunctive and supportive treatments

CQ 23. Are renin-angiotensin system (RAS) inhibitors recommended for reducing urinary protein level in nephrotic syndrome?

1. The GISEN group. Lancet 1997 ; 349 : 1857–63. (Level 2)
2. Polanco N, et al. J Am Soc Nephrol 2010 ; 21 : 697–704. (Level 2)
3. Kosmadakis G, et al. Scand J Urol Nephrol 2010 ; 44 : 251–6. (Level 2)
4. Giri S, et al. J Assoc Physicians India 2002 ; 50 : 1245–9. (Level 2)
5. Usta M, et al. J Intern Med 2003 ; 253 : 329–34. (Level 2)
6. Cheng J, et al. Int J Clin Pract 2009 ; 63 : 880–8. (Level 1)
7. Kincaid–Smith P, et al. Nephrol Dial Transplant 2002 ; 17 : 597–601. (Level 2)
8. Tomino Y, et al. J Nephrol 2009 ; 22 : 224–31. (Level 4)
9. Nakamura T, et al. Am J Hypertens 2007 ; 20 : 1195–201. (Level 2)
10. Parving HH, et al. N Engl J Med 2008 ; 358 : 2433–46. (Level 2)
11. Navaneethan SD, et al. Clin J Am Soc Nephrol 2009 ; 4 : 542–51. (Level 1)
12. Parving HH, et al. N Engl J Med 2012 ; 367 : 2204–13. (Level 2)

CQ 24. Are diuretics recommended for reducing edema in nephrotic syndrome?

1. Nakahama H, et al. Nephron 1988 ; 49 : 223–7. (Level 4)
2. Kapur G, et al. Clin J Am Soc Nephrol 2009 ; 4 : 907–13. (Level 4)
3. Ostermann M, et al. Nephron Clin Pract 2007 ; 107 : c70–6. (Level 2)
4. Felker GM, et al. N Engl J Med 2011 ; 364 : 797–805. (Level 2)
5. Fliser D, et al. Kidney Int 1999 ; 55 : 629–34. (Level 4)
6. Akcicek F, et al. BMJ 1995 ; 310 : 162–3. (Level 4)

CQ 25. Is albumin administration recommended to improve hypoalbuminemia in nephrotic syndrome?

1. Fliser D, et al. Kidney Int 1999 ; 55 : 629–34. (Level 4)

2. Ghafari A, et al. Saudi J Kidney Dis Transpl 2011 ; 22 : 471–5. (Level 4)
3. Na KY, et al. J Korean Med Sci 2001 ; 16 : 448–54. (Level 2)
4. Dharmaraj R, et al. Pediatr Nephrol 2009 ; 24 : 775–82. (Level 4)
5. Haws RM, et al. Pediatrics 1993 ; 91 : 1142–6. (Level 4)
6. Yoshimura A, et al. Clin Nephrol 1992 ; 37 : 109–14. (Level 4)

CQ 26. Are antiplatelet and anticoagulant agents recommended for reducing urinary protein level and preventing thrombosis in nephrotic syndrome?

1. Kamei K, et al. Clin J Am Soc Nephrol 2011 ; 6 : 1301–7. (Level 2)
2. Taji Y, et al. Clin and Exp Nephrol 2006 ; 10 : 268–73. (Level 1)
3. Nakamura T, et al. Nephron 2001 ; 88 : 80–2. (Level 2)
4. Nakamura T, et al. Diabetes Care 2000 ; 23 : 1168–71. (Level 2)
5. Liu XJ, et al. Intern Med 2011 ; 50 : 2503–10. (Level 1)
6. Tojo S, et al. Contrib Nephrol 1978 ; 9 : 111–27. (Level 4)
7. Zäuner I, et al. Nephrol Dial Transplant 1994 ; 9 : 619–22. (Level 2)
8. Lilova MI, et al. Pediatr Nephrol 2000 ; 15 : 74–8. (Level 4)
9. Sarasin FP, et al. Kidney Int 1994 ; 45 : 578–85. (Level 4)

CQ 27. Are statins recommended to improve dyslipidemia and life prognosis in nephrotic syndrome?

1. Ordoñez JD, et al. Kidney Int 1993 ; 44 : 638–42. (Level 4)
2. Valdivielso P, et al. Nephrology (Carlton) 2003 ; 8 : 61–4. (Level 2)
3. Fried LF, et al. Kidney Int 2001 ; 59 : 260–9. (Level 4)
4. Gheith OA, et al. Nephron 2002 ; 91 : 612–9. (Level 2)
5. Sandhu S, et al. J Am Soc Nephrol 2006 ; 17 : 2006–16. (Level 4)
6. Rayner BL, et al. Clin Nephrol 1996 ; 46 : 219–24. (Level 2)
7. Dogra GK, et al. Kidney Int 2002 ; 62 : 550–7. (Level 4)

CQ 28. Is ezetimibe recommended to improve lipid metabolism abnormalities and life prognosis in nephrotic syndrome?

1. Baigent C, et al. Lancet 2011 ; 377 : 2181–92. (Level 2)
2. Nakamura T, et al. Pharmacol Res 2010 ; 61 : 58–61. (Level 2)

CQ 29. Is low-density lipoprotein (LDL) apheresis recommended for reducing urinary protein levels in refractory nephrotic syndrome?

1. Tojo K, et al. Jpn J Nephrol 1988 ; 30 : 1153–60. (Level 5)
2. Muso E, et al. Nephron 2001 ; 89 : 408–15. (Level 4)
3. Muso E, et al. Clin Nephrol 2007 ; 67 : 341–4. (Level 4)
4. Hattori M, et al. Am J Kidney Dis 2003 ; 42 : 1121–30. (Level 5)

CQ 30. Is the extracorporeal ultrafiltration method (ECUM) recommended for refractory edema and ascites in nephrotic syndrome?

1. Smith DE, et al. J Pharm Sci 1985 ; 74 : 603–7. (Level 5)
2. Keller E, et al. Clin Pharmacol Ther 1982 ; 32 : 442–9. (Level 5)
3. Asaba H, et al. Acta Med Scand 1978 ; 204 : 145–9. (Level 5)
4. Fauchald P, et al. Acta Med Scand 1985 ; 217 : 127–31. (Level 5)

CQ 31. Is the trimethoprim-sulfamethoxazole combination recommended for preventing infectious disease during immunosuppressive therapy in nephrotic syndrome?

CQ 32. Is immunoglobulin supply recommended for preventing infectious disease in nephrotic syndrome?

1. Wu HM, et al. Cochrane Database Syst Rev 2012 ; 4 : CD003964. (Level 1)
2. Ogi M, et al. Am J Kidney Dis 1994 ; 24 : 427–36. (Level 4)

CQ 33. Is treatment with antitubercular agents recommended for preventing tuberculous infection in nephrotic syndrome?

1. Gulati S, et al. Pediatr Nephrol 1995 ; 9 : 431–4. (Level 4)
2. Gulati S, et al. Pediatr Nephrol 1997 ; 11 : 695–8. (Level 4)
3. Currie AC, et al. Transplantation 2010 ; 90 : 695–704. (Level 1)
4. Naqvi R, et al. Nephrol Dial Transplant 2010 ; 25 : 634–7. (Level 2)

CQ 34. Is immunosuppressive therapy recommended for patients with hepatitis B-positive nephrotic syndrome?

8) Lifestyle and dietary instruction

CQ 35. Is the prevalence rate of cancer in patients with membranous nephropathy higher than that in the general population?

1. Bjørneklett R, et al. Am J Kidney Dis 2007 ; 50 : 396–403. (Level 4)
2. Lefaucheur C, et al. Kidney Int 2006 ; 70 : 1510–7. (Level 4)

3. Burstein DM, et al. Am J Kidney Dis 1993 ; 22 : 5-10. (Level 5)

CQ 36. Is bed rest/exercise restriction recommended in nephrotic syndrome?

1. Fuiano G, et al. Am J Kidney Dis 2004 ; 44 : 257-63. (Level 5)

CQ 37. Is vaccination recommended in patients with nephrotic syndrome during treatment with corticosteroids and immunosuppressive drugs?

1. Fuchshuber A, et al. Nephrol Dial Transplant 1996 ; 11 : 468-73. (Level 4)
2. Collins AJ, et al. Am J Kidney Dis 2008 ; 51 : S1-320. (Level 4)

CQ 38. Are there any preventive measures against steroid-induced femoral head necrosis in nephrotic syndrome?

1. Nagasawa K, et al. Lupus 2006 ; 15 : 354-7. (Level 3)
2. Ajmal M, et al. Orthop Clin North Am 2009 ; 40 : 235-9. (Level 4)
3. Lai KA, et al. J Bone Joint Surg Am 2005 ; 87 : 2155-9. (Level 2)
4. Wang CJ, et al. Arch Orthop Trauma Surg 2008 ; 128 : 901-8. (Level 2)

CQ 39. Is the avoidance of mental stress recommended to prevent the onset and relapse of nephrotic syndrome?

1. Takahashi S, et al. J Jpn Pediatr Soc 1996 ; 100 : 72-7. (Level 4)
2. Takahashi S, et al. Pediatr Nephrol 2007 ; 22 : 232-6. (Level 4)

CQ 40. Is a fat-restricted diet recommended to improve dyslipidemia and life prognosis in nephrotic syndrome?

1. D' Amico G, et al. Clin Nephrol 1991 ; 35 : 237-42. (Level 4)
2. D' Amico G, et al. Lancet 1992 ; 339 : 1131-4. (Level 4)

2. Dietary instruction

1. Rodriguez—Iturbe B, et al. Atrial natriuretic factor in theacute nephritic and nephrotic syndromes. Kidney Int 1990 ; 38 : 512-7.
2. Kaysen GA, et al. Effect of dietary protein intake on albumin homeostasis in nephrotic patients. Kidney Int 1986 ; 29 : 572—7.
3. D'Amico G, et al. Effect of dietary proteins and lipids in patients with membranous nephropathy and nephrotic syndrome. Clin Nephrol 1991 ; 35 : 237-42.
4. Walser M, et al. Treatment of nephrotic adults with a supplemented, very low-protein diet. Am J Kidney Dis 1996 ; 28 : 354-64.
5. D'Amico G, et al. Effect of vegetarian soy diet on hyperlipidaemia in nephrotic syndrome. Lancet 1992 ; 339 : 1131-4.
6. Kopple JD, et al. Effect of energy intake on nitrogen metabolism in nondialyzed patients with chronic renal failure. Kidney Int 1986 ; 29 : 734-42.
7. Kaysen GA, et al. Effect of dietary protein intake on albumin homeostasis in nephrotic patients. Kidney Int 1986 ; 29 : 572—7.
8. Maroni BJ, et al. Mechanisms permitting nephrotic patients to achieve nitrogen equilibrium with a protein—restricted diet. J Clin Invest 1997 ; 99 : 2479-87.
9. Lim VS, et al. Leucine turnover in patients with nephrotic syndrome : evidence suggesting body protein conservation. J Am Soc Nephrol 1998 ; 9 : 1067-73.
10. Fouque D, et al. A proposed nomenclature and diagnostic criteria for protein—energy wasting in acute and chronic kidney disease. Kidney Int 2008 ; 73 : 391-8.
11. Kendirli T, et al. Vitamin B6 deficiency presenting with low alanine aminotransferase in a critically ill child. Pediatrics Int 2009 ; 51 : 597-9.
12. Nishida M, et al. Wernicke's encephalopathy in a patient with nephrotic syndrome. Eur J Pediatr 2008 ; 168 : 731-4.
13. Banerjee S, et al. Vitamin D in nephrotic syndrome remission : a case-control study. Pediatr Nephrol 2013 ; 28 : 1983-9.
14. El—Melegy NT, et al. Oxidative Modification of Low—Density Lipoprotein in Relation to Dyslipidemia and Oxidant Status in Children With Steroid Sensitive Nephrotic Syndrome. Pediatr Res 2008 ; 63 : 404-9.

3. Treatment Interpretation and Treatment Algorithm

Table1. Clinical definition of adult nephrotic syndrome

1. Proteinuria: ≥3.5 g/day and continuous
   (comparable to ≥3.5 g/gCr at spot urine)
2. Hypoalbuminemia: Serum albumin ≤ 3.0 g/dL
   Serum total protein ≤ 6.0 g/dL is helpful.
3. Edema
4. Dyslipidemia (Hyper LDL cholesterolemia)

Notes:

1) The above urine protein and hypoalbuminemia are indispensable prerequisites for the clinical diagnosis of nephrotic syndrome.
2) Edema is not an indispensable prerequisite but an important finding for nephrotic syndrome.
3) Dyslipidemia is not an indispensable prerequisite for nephrotic syndrome.
4) Oval fat body is helpful for diagnosis of nephrotic syndrome.

Table2. Therapeutic evaluation for nephrotic syndrome

The therapeutic evaluation is done by the amount of urine protein at 1 and 6 months after the initiation of treatment.

Complete remission: urine protein <3.0 g/day

Incomplete remission I: 0.3 g/day ≤ urine protein <1.0 g/day

Incomplete remission II: 1.0 g/day ≤ urine protein <3.5 g/day

Non-response: urine protein ≥3.5 g/day

Notes:

1) The diagnosis of nephrotic syndrome and therapeutic evaluation should be done by 24-hour urine collection. If to collect 24-hour urine is impossible, the ratio of urine protein and urine creatinine (g/gCr) at spot urine is available for the diagnosis of nephrotic syndrome and therapeutic evaluation.
2) In principle, the evaluation of complete remission or incomplete remission at 6 months after the initiation of treatment includes the improvement of clinical finings and serum albumin.
3) The evaluation of relapse is the condition that urine protein ≥ 1 g/gCr (1g/gCr) runs or ≥ (2+) continues 2～3 times in a row.
4) In Europe and the United States partial remission defines 50% or more of the reduction of urine protein, while the Japanese evaluation does not use this definition.

Table3. The classification by the response to treatment of nephrotic syndrome

Steroid resistant nephrotic syndrome: The enough dose of steroid treatment fails to achieve complete remission or incomplete remission I at 1 month after the initiation of treatment.

Refractory nephrotic syndrome: The various treatments including steroid and immunosuppressive agents fail to achieve complete remission or incomplete remission I at 6 months after the initiation of treatment.

Steroid dependent nephrotic syndrome: Steroid treatment is impossible to discontinue, because repeated over 2 times relapses appear after the reduction or discontinuation of steroid.

Frequent relapse nephrotic syndrome: Over 2 times relapses appear in 6 months.

Nephrotic syndrome requiring chronic treatment: Nephrotic syndrome to be treated by steroid or immunosuppressive agents over 2 years.

Table4. The definition of nephrotic syndrome in children

1. Nephrotic syndrome: Massive proteinuria (40 ≥ mg/h/m^2) + hypoalbuminemia (serum albumin ≤ 2.5 g/dL)
2. Steroid sensitive nephrotic syndrome: Daily administrated prednisolone treatment attains the remission within 4 weeks.
3. Relapse: After the remission urine protein of 40 ≥ mg/h/m^2 or morning urine 100 mg/dL or more by dip stick continues for 3 days.

Table5. Examination findings of primary nephrotic syndrome

Examination	Measurement items	Major findings
Urinalysis	urine volume, urine protein (24-h collection or spot urine) fraction of urine protein occult blood, urinary sediments granular cast, waxy cast selectivity of urine protein (clearance ration of IgG and transferrin)	increase: urine protein, albuminemia fatty cast, oval fat body
Blood examination	peripheral blood examination	sometimes decrease: red blood cell, hemoglobin
	biochemical examination	decrease: total protein, albumin sometimes decrease: Na, vitamin D, GFR sometimes increase: BUN, Cr
	lipid examination	increase: total cholesterol, LDL, VLDL,La(a) ApoB, ApoC II , HDL-3 stable: HDL decrease: HDL-2
	coagulation test	increase: fibrinogen, FDP, D-dimer decrease: antithrombin III, plasminogen
	immunological test	decrease: IgG and other immunoglobulins, complements
Chest X-ray	cardiothoratic ratio, pulmonary vascular shadow cost-phrenic angle shadow of lung field	sometimes: pulmonary congestion
Ultrasonography	deep vein thrombosis in lower extremities	collapse of venous system due to decrease of circular blood volume
Renal biopsy	light microscopy immunofluorescence microscopy electron microscopy	The definitive diagnosis is usually determined by renal biopsy.

Notes: When secondary nephrotic syndrome is suspected from patient's conditions, the examinations according to each baseline disease should be added. (For example: In the case of lupus nephritis, the examinations concerning collagen diseases should be done as additional items.)

Table6. Examination findings of secondary nephrotic syndrome

Examination	Measurement items	Major findings
Urinalysis	occult blood urine Bence Jones protein	positive in purpura nephritis or vasculitis positive in paraproteinemia
Blood examination	peripheral blood examination	pancytopenia or hemolytic anemia in lupus nephritis leukocytosis and thrombocytosis in the cases with infectious diseases ad vasculitis
	biochemical examination	blood sugar markers such as blood glucose, HbA1c, and glycoalbumin in diabetic nephropathy. CRP and inflammatory reactions increase in in vasculitis and purpura nephritis. Paraprotein or cryoglobumin is confirmed in in the cases with paraproteinemia.
	lipid examination	The abnormality of IDL or ApoE is confirmed in lipoprotein glomerulopathy.
	immunological examination	Anti-nuclear antibody , anti-ds-DNA antibdy, anti-Sm antibody, anti-phosphlipid antibody increase and complements decrease in lupus nephritis. The positive findings are confirmed in bacterial culture and antigen/antibody detection for pathogenic microbes.
Renal biopsy		The specific findings are observed in each secondary disease, thus the renal biopsy is useful for the definitive diagnosis of secondary diseases.
Imaging test		Neoplastic diseases are diagnosed by various imaging tests such as CT, MRI, ultrasonography and bone marrow aspiration.
Genetic test		Genetic tests are useful in the genetic illnesses

Fig. 1. Treatment of MCNS

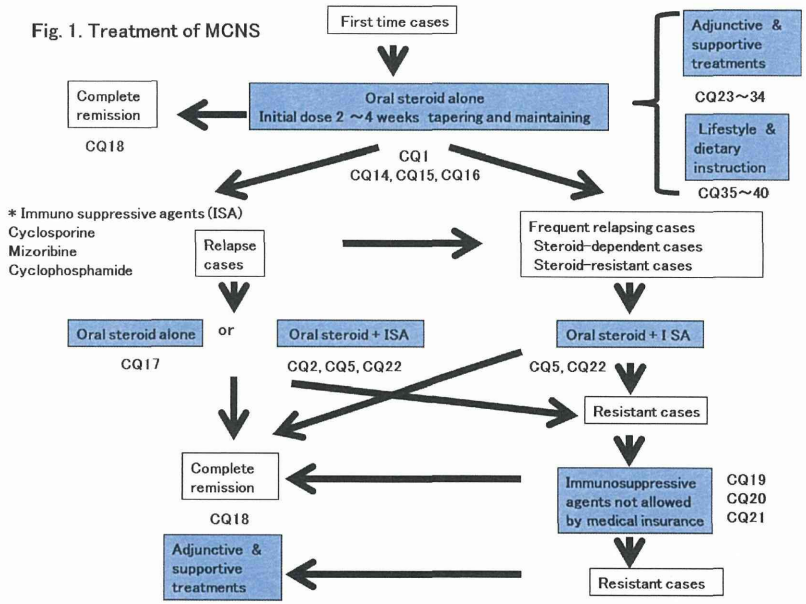


Fig. 2. Treatment of FSGS

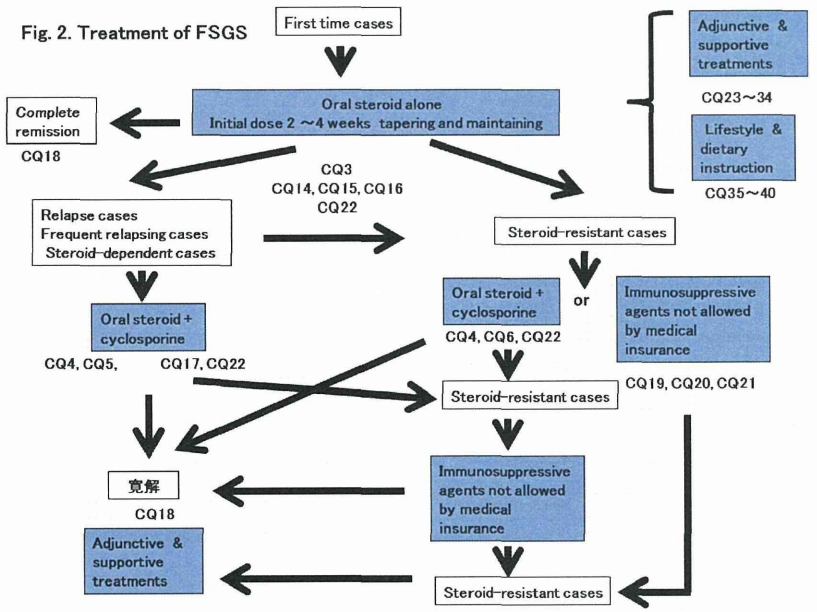
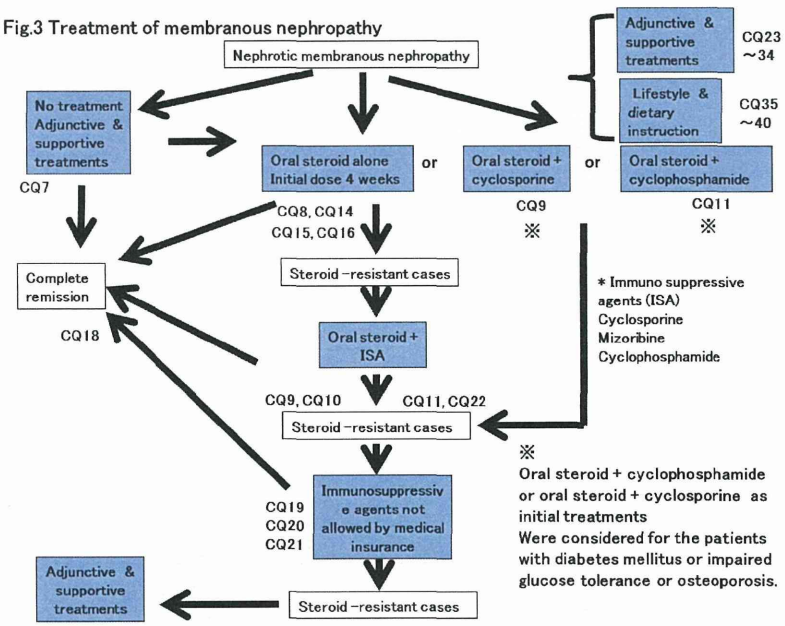


Fig.3 Treatment of membranous nephropathy



Evidence-Based Clinical Practice Guidelines for Polycystic Kidney Disease 2014

July 27th, 2015

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Cooperative Medical Society

The Japanese Urological Association
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The Japanese Society for Pediatric nephrology

The Japan Society of Human Genetics
The Japan Neurosurgical society
The Japanese Association for Infectious disease
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The Japan Society for Transplantation

Preface

1. Origins of the Guidelines

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease, with approximately half of the patients experiencing end-stage renal disease by age 60. Bilateral cysts progressively proliferate and enlarge, even as complications such as hypertension, hepatic cysts, and intracranial aneurysms lead to more lethal events such as cyst infections and ruptured intracranial aneurysms prior to end-stage renal disease. Early-stage diagnosis and intervention are recognized as being vital. Autosomal recessive polycystic kidney disease (ARPKD) is estimated to occur in 1 in 10,000~40,000 births, with symptoms present neonatally. Due to early detection and management as well as improvements in end-stage renal disease treatment, long-term survival is currently possible in patients other than neonates with severe pulmonary hypoplasia.

In Japan, Clinical Guidelines for Polycystic Kidney Disease in 1995 was published by the Progressive Renal Diseases Research, Research on intractable disease, from the Ministry of Health, Labour and Welfare of Japan, followed by a 2002 revision, the ADPKD Guidelines (second edition). Both serve as protocols for daily treatment of ADPKD in Japan. However, subsequent advancements in PKD expertise led to the 2010 Clinical Guidelines for Polycystic Kidney Disease, which were aimed at physicians and other health practitioners. These events provided the backdrop for the 2014 Clinical Practice Guidelines for Polycystic Kidney Disease, which were drawn up to answer the questions of physicians specializing in renal care.

2. The Intended Purpose, Anticipated Users, and Predicted Social Significance of the Guidelines

The 2014 Clinical Practice Guidelines for Polycystic Kidney Disease were drawn up to assist renal care specialists with daily diagnosis and treatment of ADPKD and ARPKD. These Guidelines offer descriptive and exhaustive coverage of PKD diagnosis and definition, epidemiology, and screening. Moreover, routine treatment by renal specialists is addressed through clinical questions (CQs) and responses. Each response is accompanied by a recommendation grade reflecting the level of evidence the response embodies. Our objective is to convey standardized care through specific responses to

renal specialists' questions, thereby supporting these professionals as they face daily clinical decisions. We anticipate that general practitioners using the current Guidelines along with the 2010 Clinical Guidelines for Polycystic Kidney Disease will deepen their understanding of PKD and liaise more smoothly with renal specialists. The Guidelines should also enhance patients' understanding of the disease and serve as a reference in answering their questions concerning current treatments.

Professional literature and international conferences afford renal specialists fragmented bits of information about the field, while the specialists are expected to have an integrated understanding of the expertise level and medical environment in Japan, and to provide optimal care for each patient. The current Guidelines incorporate the wisdom of experienced specialists, offering not only evidence, but also practical and standardized views communicated to readers through the CQ responses. However, the degree to which information in these Guidelines may be applied to individual patients requires the judgment of each specialist. Patients do not expect uniform, rigid treatment. Indeed, these Guidelines are not intended to restrict the treatment options available to renal specialists, but rather to facilitate treatment based on their own flexible insights and expert understanding. We must also clarify that the Guidelines are not designed for use in resolving medical practice disputes or as evaluation criteria in malpractice lawsuits.

3. Patients within the Scope of the Guidelines

These Guidelines apply to any and all PKD patients. Sections 1~4 address ADPKD, whereas Sections 5~9 cover ARPKD. The Guidelines provide an outline and definition (Sections 1 and 5) for each of the two diseases, along with information on diagnosis (Sections 2 and 6), epidemiology (Sections 3 and 7), and treatment (Sections 4 and 9). Each section applies to patients regardless of gender or age. However, the Guidelines do not generally take pregnancy into account.

4. Preparation procedure

Guidelines on four diseases (IgA nephropathy, nephrotic syndrome, RPGN, and polycystic kidney disease [PKD]) were created simultaneously by a research group on progressive kidney disorders (led by Seiichi Matsuo) funded by the Ministry of Health, Labour, and Welfare's research project for overcoming intractable diseases. All of these guidelines have the same chapter structure. PKD is a genetic disease, so Shinshu University professor Yoshimitsu Fukushima assisted by serving on the drafting committee as a representative of the Japan Society of Human Genetics. Keiichi Furukawa of the Division of Infectious Diseases in the Department of Internal Medicine at St. Luke's International Hospital provided assistance regarding cyst infections. We would like to take this opportunity to thank these two physicians for their generous help.

Seventeen CQ were created based on questions the committee members had from actual clinical practice. These guidelines were completed owing to the dedication and effort of the physicians who served on the PKD working group. We thank them again for their efforts. (shown separately: 2014 evidence-based PKD clinical guidelines committee)

5. Contents of the guideline

Guidelines on four diseases (IgA nephropathy, nephrotic syndrome, RPGN, and PKD) with the same format and structure were drafted by a research group on progressive kidney disorders (led by Seiichi Matsuo) funded by the Ministry of Health, Labour, and Welfare's research project for overcoming intractable diseases. As described earlier, the first half (chapters 1–4) addresses ADPKD and the second half (chapters 5–8) addresses ARPKD.

6. Evidence Levels and Recommendation Grades

Evidence was classified into six levels based on the study design, and was arranged roughly from the most reliable study type (Level 1) to the least reliable (Level 6). These levels do not necessarily represent rigorous scientific standards; they are intended for use as a convenient reference for quickly assessing the significance of various clinical data during the physician's decision-making process.

[Evidence Levels]

Level 1: Systematic review/meta-analysis

Level 2: At least one randomized controlled trial (RCT)

Level 3: A non-RCT

Level 4: An analytical epidemiologic study (cohort study or case-control study) or a single-arm intervention study (no controls)

Level 5: A descriptive study (case report or case series)

Level 6: Opinion of an expert committee or an individual expert, which is not based on patient data

However, for a systematic review/meta-analysis, the evidence level was decided based on the designs of the underlying studies. If the underlying study designs were mixed, the lowest level underlying study was used to determine the overall evidence level. For example, a meta-analysis of cohort studies would be Level 4, but the same Level 4 would also be assigned to a meta-analysis including both RCTs and cohort studies.

In addition, a decision based on committee consensus was that all sub-analyses and post-hoc analyses of RCTs should be categorized at evidence Level 4. Accordingly, it was decided that the evidence level of findings representing the primary endpoints of an RCT would be Level 2, but the evidence level of findings determined via a sub analysis or post-hoc analysis of that RCT would be Level 4.

When a statement related to a certain treatment was presented, consideration was given to the level of the evidence serving as the basis of that statement, and a recommendation grade was assigned as outlined below:

[Recommendation Grades]

Grade A: Strongly recommended because the scientific basis is strong.

Grade B: Recommended because there is some scientific basis.

Grade C1: Recommended despite having only a weak scientific basis

Grade C2: Not recommended because there is only a weak scientific basis

Grade D: Not recommended because scientific evidence shows the treatment to be ineffective or harmful.

If we found only a weak scientific basis for a certain statement concerning a treatment, the members of the committee discussed the matter and decided on C1 or C2 for the recommendation grade. Thus, discrimination between C1 and C2 statements was based on expert consensus.

7. Issues on the preparation of this guideline

(1) Paucity of evidence

Little evidence exists for PKD, and only few large clinical studies have been performed globally, apart from a small number in the United States and Europe. For the most part, little evidence substantiates the recommendations in the CQ. In particular, almost no evidence comes from Japan. Whether the results of clinical research from the West can be applied as is to Japan is a question that deserves careful consideration. In creating these guidelines, we strove to ensure that they would not deviate greatly from the clinical practice in Japan.

(2) Issues on medical resources

In general, the clinical guideline must consider medical resources associated with recommended statements. However, the current guideline did not discuss issues on medical cost; thus medical financial problems did not affect the contents of our guideline. In the next guideline, this point may be included.

(3) Guideline reflecting the opinions of patients

During the preparation processes of the clinical guideline, we needed to introduce the opinions of patients. However, this time, we unfortunately could not include the opinions of patients. We should refer to the opinions of patients in the next guideline, particularly in the case that the guideline is used for patients.

8. Financial sources and conflict of interest

The funds used in creating the guidelines were provided by a research group on progressive kidney disorders funded by the Ministry of Health, Labour, and Welfare's research project for overcoming intractable diseases. These funds were used to pay for transportation to and from meetings, to rent space for meetings, and for box lunches and snacks. The committee members received no compensation. Everyone involved in creating the guidelines (including referees) submitted conflict-of-interest statements based on academic society rules, which are managed by JSN. Opinions were sought from multiple referees and related academic societies to prevent the guidelines from being influenced by any conflicts of interest. Drafts were shown to the society members, and revisions were made based on their opinions (public comments).

9. Publication and Future Revisions

The Guidelines were published in the Japanese-language journal of the Japanese Society of Nephrology and concurrently released as a Japanese-language book (by Tokyo Igakusha, Tokyo). The Guidelines were also uploaded to the homepage of the Japanese Society of Nephrology.

At present, CKD-related evidence is being rapidly accumulated, and this new evidence will necessitate the preparation of an updated version of the

Guidelines in 3-5 years. A certain degree of turnover in the membership of the revision committee will be required in order to ensure the impartiality of the Guidelines.

Content

ADPKD patients?

CQ 7. Is treatment recommended for cerebral aneurysms detected during screening?

2) Cyst infection

CQ 8. Are newer quinolones recommended for the treatment of cyst infection in ADPKD?

3) Cystic hemorrhage/hematuria

CQ 9. Should we recommend tranexamic acid in the treatment of cystic hemorrhage in ADPKD?

4) Urolithiasis

CQ 10. Are there any effective pharmacological preventive therapies for urolithiasis associated with ADPKD?

5) Cardiac complications (including valvular disease)

CQ 11. Is transthoracic echocardiography (TTE) for screening of valvular disease recommended to improve the mortality of ADPKD patients?

6) The specific treatment of complications

CQ 12. Should ADPKD patients with ESRD undergo renal transarterial embolization to reduce enlarged kidneys?

CQ 13. Should ADPKD patients with ESRD undergo hepatic transarterial embolization to reduce hepatomegaly?

3. The treatment of ESRD

1) Peritoneal dialysis

CQ 14. Is peritoneal dialysis recommended for patients with ADPKD?

2) Renal transplantation

CQ 15. Is unilateral or bilateral nephrectomy recommended during ADPKD kidney transplantation?

V. Autosomal Recessive Polycystic Kidney Disease (ARPKD): Disease concept/definition (etiology and pathophysiological mechanism)

VI. ARPKD: Diagnosis (symptomatology, symptom, and examination findings)

VII. ARPKD: Epidemiology and prognosis (incidence, prevalence, and treatment outcome)

1. ARPKD: Prenatal diagnosis

2. ARPKD: Treatment and management of complications (treatment of disease including adjunct therapy, supportive therapy, and prophylaxis)

CQ 16. Is peritoneal dialysis recommended for the improvement of the vital prognosis and quality of life (QOL) of patients with ARPKD?

CQ 17. Is solitary or simultaneous transplantation of the liver and kidney recommended for the improvement of the vital prognosis and QOL of patients with ARPKD?

CQ 18. Is antihypertensive therapy recommended for the improvement of the vital prognosis of patients with ARPKD?

1. Disease concept and definition of ADPKD

ADPKD is the most common hereditary cystic kidney disease. ADPKD is characterized by the progressive development of fluid-filled cysts derived from renal tubular epithelial cells and the development of disorders in several organs. Bilateral renal cysts enlarge progressively, gradually compromising renal function, and finally, end-stage renal disease (ESRD) requiring renal replacement therapy occurs in approximately 50% of patients by the age of 60 years.

The pattern of transmission in ADPKD is autosomal dominant inheritance. A male or female with a mutant allele develops the disease. In case that both parents are unaffected, disease in the offspring results from new mutation.

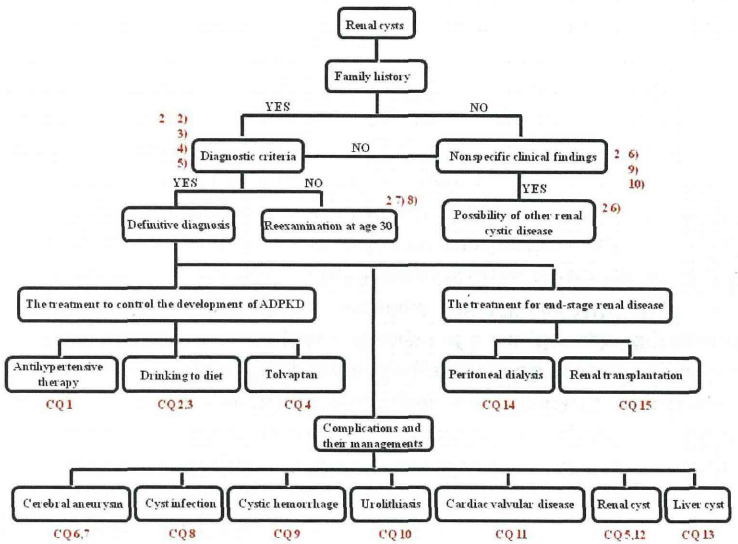
ADPKD is caused by a germ line mutation in *PKD1* (16p13.3)(85% of cases) or *PKD2* (4q21)(15% of cases).

2. Diagnosis of ADPKD: Symptoms and laboratory findings

1) Algorithm

The diagnostic algorithm for ADPKD is depicted in the figure. Family history, while important in ADPKD diagnosis, often cannot be assessed. Moreover, even in the absence of family history, it is important to remain alert to newly reported mutations in *PKD1*/*PKD2* genes responsible for disease onset. It can be difficult to detect cysts meeting diagnostic criteria in younger patients, requiring reexamination. Clinical questions (CQs) are appended to these guidelines as a reference in following the algorithm and determining treatment and other medical care once a definitive diagnosis has been made.

Figure



2) Diagnostic criteria

Table 1 presents the diagnostic criteria of ADPKD (*ADPKD Diagnostic Guidelines, Second Edition*, published by a Grant-in-Aid for Progressive Renal Diseases Research, Ministry of Health, Labour and Welfare of Japan). Confirmation or nonconfirmation of family history determines one of two possible protocols, each requiring its own distinctive cyst assessment based not only on ultrasonography (US) but also on computed tomography (CT) and magnetic resonance imaging (MRI). In most cases, cysts manifest bilaterally and diagnosis is uncomplicated; in the remaining cases, diagnosis should be carefully performed in accordance with the diagnostic criteria noted herein.

Table 1 the diagnostic criteria of ADPKD (*ADPKD Diagnostic Guidelines, Second Edition*, published by a Grant-in-Aid for Progressive Renal Diseases Research, Research on intractable disease, from the Ministry of Health, Labour and Welfare of Japan)

1. Confirmation of family history
a. Three or more bilaterally-manifested cysts confirmed with ultrasonography
b. Five or more bilaterally-manifested cysts confirmed with CT and MRI imaging
2. Non-confirmation of family history
a. Patients 15-years old or younger: three or more bilaterally-manifested cysts confirmed with either CT and MRI imaging or ultrasonography
b. Patients 16-years old or older: five or more bilaterally-manifested cysts confirmed with either CT and MRI imaging or ultrasonography
Diseases to be excluded
1. Multiple simple renal cyst
2. Renal tubular acidosis
3. Multicystic kidney (multicystic dysplastic kidney)
4. Multilocular cysts of the kidney
5. Medullary cystic disease of the kidney (juvenile nephronophthisis)
6. Acquired cystic disease of the kidney
7. Autosomal recessive polycystic kidney disease

3) Comparison of diagnostic criteria between Japan and other countries

Following Bear's diagnostic criteria in 1984, numerous other versions have been reported, each with its own emphasis on, for example, age classification or cyst assessment through imaging. Ravine's criteria, which were utilized for some time, were the first guidelines reflecting age as a factor. However, Ravine only incorporated *PKD1* family history. Although *PKD1* and *PKD2* mutations each result in almost the same clinical manifestation of the disease, *PKD1* progresses to ESRD more rapidly and produces more cysts, leading Pei to incorporate both *PKD1* and *PKD2* families in his diagnostic criteria. Diagnosis in Western countries combining US with genetic testing is highly credible and should serve as a reference, but its applicability to Japanese patients has not yet been demonstrated.

4) Testing

ADPKD screening should include family history of renal disease (end-stage and otherwise) and intracranial hemorrhage/cerebrovascular disease; patient history of hypertension, cerebrovascular disease, urinary tract infection, fever, and lower back pain; subjective symptoms such as macroscopic hematuria, lower back and/or flank pain, abdominal distension, headache, edema, and nausea; physical examination to determine blood pressure, abdominal girth, heartbeat, abdominal findings, and edema; blood and urine tests, screening for urinary sediment, proteinuria, and microalbuminuria; estimated glomerular filtration rate (eGFR) and other renal function tests; and screening for intracranial aneurysm through cranial MR angiography. US represents the simplest form of diagnostic imaging for kidney diseases. Other tests to be performed, as appropriate, should include measurement of *N*-acetyl beta-glucosaminidase and urinary beta2 microglobulin values, MRI, and kidney CT imaging.

5) Diagnostic imaging

US is the standard screening technique for ADPKD diagnosis and evaluation, but evaluation of kidney size, as opposed to function, is reportedly the better measurement in the evaluation of progression, with CT or MRI recommended for follow-up evaluation. The latter methods surpass US in detecting smaller cysts; MRI can detect cysts with a diameter of 2 mm through T2-weighted imaging. Each diagnostic imaging technique (US, CT, and MRI) plays a role in highlighting the distinctive characteristics of cysts. Diagnostic imaging is also clinically important in terms of disease complications such as cerebral aneurysms. As adverse reactions can occur, careful consideration must be given to the risk–benefit balance before utilizing contrast media. MRA is useful in screening for cerebral aneurysms and is a noninvasive test with the great benefit of not requiring contrast media. If imaging performed after a definitive ADPKD diagnosis is strictly for follow-up observation, a simple CT once every 2–5 years would be adequate if total kidney volume (TKV) is ≤1,000 mL. If TKV exceeds 1,000 mL, CT once every year or two would be appropriate. For screening purposes, diagnostic imaging at the age of 30 years

is recommended.

6) Differential diagnosis

A patient's clinical manifestation and diagnostic imaging should be used to rule out possibilities such as multiple simple renal cysts, acquired cystic kidney disease, and tuberous sclerosis (Table 2). Particular caution is needed when considering tuberous sclerosis, as approximately 30% of patients with this disease are said to have no typical symptoms other than renal cysts, which are mistakenly attributed to ADPKD. Additional diseases to be ruled out include renal tubular acidosis, multicystic kidney (multicystic dysplastic kidney), multilocular cyst of the kidney, medullary cystic kidney disease, and oral–facial–digital syndrome. As rare diseases are difficult to identify and distinguish during normal medical examinations, despite reports on characteristic indicators other than renal cysts, extra care should be given during differential diagnosis.

Table 2 Major non-ADPKD renal cystic diseases

Disease	Cyst proliferation	Cyst distribution/size	Typical life stage for cyst diagnosis	Pathophysiological characteristics
Multiple simple renal cyst	Moderate	Size diversity/non-uniform distribution	All ages	Rare under age 30 years; manifestation increases with age
Acquired cystic disease of the kidney	Moderate to great	Diffusibility	Adulthood	Cyst formation precedes ESRD
Tuberous sclerosis	Moderate to great	Uniform distribution of relatively small (<1 to 2 cm) cysts	All ages	Renal angiomyolipomas, skin lesions, periungual fibromas, retinal hamartomas, and cardiac rhabdomyomas
ARPKD	Great	Diffusibility/small cysts	Birth	Greatly enlarged kidney, congenital hepatic fibrosis

7) Genetic diagnosis

ADPKD is an autosomal dominant genetic disease. Responsible genes for ADPKD were already identified. Diagnosis of ADPKD in typical cases is easy by detecting multiple cysts in both kidneys.

In Japan, genetic diagnostic tests for ADPKD are only available for basic research but not for clinical practice. Physicians must consider whether samples for genetic testing should be sent to foreign laboratories.

8) Diagnostic imaging for infants and young adults

Diagnostic criteria, including imaging, for ADPKD in infants and young adults have not been established. Screening imaging tests are not recommended for nonsymptomatic infants and young adults, even if they are children of ADPKD patients.

9) Initial symptoms

Cysts are said to form in utero, with most progressing asymptomatically until the patients are in their 30s or 40s. Subjective symptoms include abdominal or lower back pain, macroscopic hematuria (including its posttraumatic form caused by sports activities), or abdominal bloating. Acute pain is usually attributable to hemorrhagic cysts, infection, or urinary tract stones. Chronic pain is defined as persistent pain for 4–6 weeks. It occurs in approximately 60% of ADPKD cases and is usually attributable to cysts. Macroscopic hematuria occurs in approximately 50% of all cases. Hypertension, diagnosed objectively by physical examination and other methods, is a significant initial symptom (or findings).

10) Renal symptoms

Both acute and chronic abdominal and/or flank pain is one of the most prevalent subjective symptoms of ADPKD, whereas many patients do not have any complaint until their third or fourth decade of life. Anorexia, gastrointestinal obstruction, and malnutrition are manifestations of compression of the gastrointestinal tract by the advanced enlargement of the kidney (and/or the liver). Macroscopic hematuria is observed at least once during the entire clinical course in almost 50% of the patients. Massive proteinuria is rare. The first functional abnormality of the kidney is disturbed concentrating capacity, although it rarely becomes clinically evident unless

the patient complains of polydipsia and polyuria. Decrease in GFR usually starts after 40 years of age, and the mean rate of its reduction is 4.4–5.9 mL/(min·year).

The factors associated with rapid progression of GFR decline have been reported as follows:

① Disease-causing gene (worse in cases with *PKD1* mutation than in those with *PKD2* mutation)
② Hypertension
③ Early development of urinary abnormality (hematuria and proteinuria)
④ Male sex
⑤ Large size and rapid enlargement of the kidney
⑥ Left cardiac hypertrophy
⑦ Proteinuria

3. ADPKD: Epidemiology and prognosis (prevalence, incidence, renal prognosis, and vital prognosis)

The number of ADPKD patients in Japan who visited hospitals was estimated to be 14,594, yielding an ADPKD prevalence of 116.7 cases per million population at the end of 1994. The total number of ADPKD patients including those who will visit hospitals in the future was estimated to be 31,000. It was suggested that ADPKD affected 1 individual per 4033 population in Japan. ADPKD was diagnosed in 40 residents of Olmsted County between 1935 and 1980, resulting in an age- and sex-adjusted annual incidence rate of 1.38 case per 100,000 person-years. Approximately 50% of the patients developed ESRD at the age of 60–69 years. The most common causes of death in ADPKD were infection, sepsis, and cardiac disease (myocardial infarction and congestive heart failure). The survival of ADPKD patients undergoing dialysis surpasses that of general dialysis patients.

4. ADPKD: Treatment and management of complications

1) Treatment to control the development of ADPKD

CQ 1. Is antihypertensive treatment recommended as a means of slowing the deterioration of renal function in patients with ADPKD complicated with hypertension?

Recommendation Grade: C1

Antihypertensive treatment is recommended for patients with ADPKD complicated with hypertension to slow the deterioration of renal function.

[Summary]

Hypertension in ADPKD is frequent and develops at a young age, in contrast to essential hypertension. In addition, it is often detected when renal function is normal and cysts are still small. Antihypertensive treatment is generally performed. It is thought that antihypertensive treatment may slow the deterioration of renal function in ADPKD with hypertension. However, because the evidence related to the recommended antihypertensive agents and target blood pressure is inconclusive, we recommend that antihypertensive treatment in ADPKD should follow that administered for chronic kidney disease (CKD).

CQ 2. Does increased water intake have a beneficial effect in ADPKD patients?

Recommendation Grade: C1

Human studies of high water intake to affect the progression of renal dysfunction in ADPKD patients have not been reported; however, drinking water can affect the progression of ADPKD by suppressing ADH, resulting in attenuation of cyst growth and proliferation of cystic cells. Thus, 2.5 – 4 L/day of water intake would be recommended for ADPKD.

[Summary]

A 3′-5′-cyclic adenosine monophosphate (cAMP)-mediating vasopressin receptor can stimulate cystic cell proliferation and fluid secretion into cysts in ADPKD. Thus, a novel treatment of ADPKD that targets the vasopressin-cAMP axis is currently evaluated and a selective inhibitor of vasopressin 2 receptor is adopted and examined for its effects on ADPKD. Another way to suppress vasopressin secretion is to increase fluid intake to mediate osmoregulation. Although human studies have not been reported regarding the effect of high water intake on the renal size and function of ADPKD, increasing water intake could be recommended to affect the progression of ADPKD based on the biological properties of the cystic epithelium. A larger human study is needed to clarify the effect of high water intake; patients would be advised to avoid stimulating vasopressin secretion by chronic water depletion.

CQ 3. Should we recommend dietary protein restriction (DPR) to inhibit progression of renal dysfunction in patients with ADPKD?

Recommendation Grade: C1

Evidence is limited and unclear whether DPR is effective for inhibiting progression of renal dysfunction in patients with ADPKD; however, it may considered.

[Summary]

The effect of DPR on ADPKD has been examined by several clinical studies, including small retrospective studies and randomized clinical trials. However, almost all studies have shown no significant effect of DPR on the progression of renal dysfunction. Although a meta-analysis showed the efficacy of DPR in patients with CKD, including ADPKD, the effect in ADPKD patients alone was not evaluated. However, we could not conclude that DPR is ineffective for those patients because of the many limitations of those clinical studies, such as a small sample size, low prevalence of outcome due to a short observation period, and low adherence to DPR. Thus, further evidence is required to answer this question.

CQ 4. Is tolvaptan recommended for treatment of ADPKD?

Recommendation Grade: B

Tolvaptan slow the increase in total kidney volume and the decline in kidney function in ADPKD patients with a relatively-good renal function with creatinine clearance ≥60 mL/min by Cock-Croft equation and a total kidney volume of 750 ml or more. Therefore, tolvaptan is recommended for treatment of ADPKD.

[Summary]

Tolvaptan, a V_2-receptor antagonist, selectively blocks the binding of vasopressin to the V2-receptors and inhibit production of cAMP. To determine the effect of tolvaptan to suppress the increase in total kidney volume, a phase 3, international multicenter, double-blind, placebo-controlled, 3-year trial (TEMPO3/4) was performed. The results of the trial demonstrated that tolvaptan slowed the increase in total kidney volume and the decline in kidney function in ADPKD patients with a relatively-good renal function with creatinine clearance ≥60 mL/min by Cock-Croft equation and a total kidney volume of 750 ml or more. Due to the lack of other specific and efficacious treatments for ADPKD at present time, with particular attention to serious adverse events such as drug-induced liver injury, tolvaptan is recommend for treatment of ADPKD patients with a relatively-good renal function and a total kidney volume of 750 ml or more. However, the safety of tolvaptan therapy for adult patients with creatinine clearance <60 mL/min or total kidney volume less than 750 mL or children is not established.

CQ 5. Aspiration of renal cysts in patients with ADPKD

Recommendation Grade: C1

Aspiration of renal cysts for ADPKD is not recommended for improving renal function. The procedure would be considered in the management of disease-related chronic pain or abdominal distention, as well as for diagnostic purposes and the treatment of infected cysts.

[Summary]

A review of cyst aspiration and surgical cyst decortication for symptomatic ADPKD was performed. The impact of renal cyst aspiration or surgical cyst decortication on renal function and hypertension in patients with ADPKD is controversial, but these procedures are highly effective in the management of disease-related chronic pain. The duration of pain relief is shorter in cyst aspiration than surgical cyst decortication.

The cyst aspiration technique for simple renal cysts can be used for ADPKD. Cyst aspiration followed by instillation of a sclerosing agent (most commonly ethanol) is indicated when the symptoms are caused by one or few dominant or strategically located cysts. Cyst aspiration and sclerosis for multiple cysts need further investigation.

Cyst aspiration for diagnostic purposes and the treatment of infected cysts has been the standard procedure.

CQ 6. Does screening of intracranial aneurysms improve the prognosis of ADPKD patients?

Recommendation Grade: B

The prevalence of unruptured intracranial aneurysms in ADPKD patients is higher than that in the general population. Intracranial hemorrhage, either cerebral or aneurysmal subarachnoid hemorrhage (SAH), confers high risks for mortality and morbidity in ADPKD patients. Screening of intracranial

aneurysms improves prognosis.

[Summary]

The high incidence of intracranial aneurysms in patients with ADPKD has long been recognized. Rupture of an intracranial aneurysm resulting in SAH is the most devastating extrarenal complications and often results in premature death or disability. The prevalence rate of unruptured intracranial aneurysms in patients with ADPKD is higher than that in people without comorbidity. First-degree relatives (parents, siblings, and children) of patients with subarachnoid hemorrhage have a 3–7 times higher risk for SAH than the general population.

Aneurysm size correlates with the presence of symptoms and the risk of bleeding, and aneurysms may rupture more often and at a younger age than sporadic aneurysms. However, there is no correlation between the risk of rupture and sex, renal function and blood pressure. Hence, it is difficult to predict intracranial aneurysm rupture.

Intracranial hemorrhage, either cerebral hemorrhage or aneurysmal SAH, confers high risks for mortality and morbidity in PKD patients. Screening of intracranial aneurysms improves prognosis.

CQ 7. Is treatment recommended for cerebral aneurysms detected during screening?

Recommendation Grade: C1

Treatment of a cerebral aneurysm is determined by a comprehensive examination of factors such as location, shape, and size of the aneurysm, and general conditions, age, and medical history of the patient. Decisions regarding treatment advisability and method should follow consultation with a neurosurgeon.

[Summary]

Considering that a ruptured cerebral aneurysm is a life-threatening complication, detection of an unruptured cerebral aneurysm during screening should receive all due attention. However, there is no particular treatment for the latter, which is specific to ADPKD. Detection of a cerebral aneurysm during screening should be followed by careful control of smoking, alcohol consumption, and blood pressure. Treatment of a cerebral aneurysm is surgery, involving a craniotomy and endovascular treatment, with specifics determined following comprehensive investigation of the location, shape, and size of the aneurysm, and general conditions, age, and medical history of the patient. As treatment options have their respective strengths and weaknesses, decisions should follow consultation with a neurosurgeon. If conservative observation is chosen, biannual—or at the very least, annual—monitoring of aneurysm size is recommended.

CQ 8. Are newer quinolones recommended for the treatment of cyst infection in ADPKD?

Recommendation Grade: C1

Administration of the newer quinolones is recommended for the treatment of cyst infection in ADPKD.

[Summary]

Cyst infection is a frequent and serious complication of ADPKD and is often refractory and difficult to treat. Most causative bacteria originate from the intestine, and many are gram-negative rods. Fluoroquinolones, which have broad effectiveness against gram-negative rods and good penetration of cysts, is recommended for the treatment of infected cysts in ADPKD. Having said this, however, there has not been an adequate level of study to investigate the actual effectiveness of fluoroquinolones for treating cyst infection in ADPKD. Few studies have compared fluoroquinolones with other antibiotics for the treatment of cyst infection in ADPKD.

CQ 9. Should we recommend tranexamic acid in the treatment of cystic hemorrhage in ADPKD?

Recommendation Grade: C1

Tranexamic acid may be considered when cystic hemorrhage does not improve by conservative treatment.

[Summary]

Hematuria is a common problem in patients with polycystic kidney disease. It can be spontaneous or result from trauma, renal calculi, tumor, or infection. These episodes are normally managed with conservative medical treatment and rarely require surgery or embolization. Only a few published studies have investigated the use of tranexamic acid for the treatment of cystic hemorrhage in ADPKD. However, these studies demonstrated that tranexamic acid can be used safely and is effective for selected ADPKD

patients with severe or intractable cystic hemorrhage that does not respond to conventional treatment.
Thus, tranexamic acid may be considered when cystic hemorrhage does not improve by conservative treatment.

CQ 10. Are there any effective pharmacological preventive therapies for urolithiasis associated with ADPKD?

Recommendation Grade: C1
Because of the lack of data about the prophylactic efficacy for urolithiasis in patients with ADPKD, we cannot recommend any medical treatment to provide a prophylactic benefit. We may recommend, however, the standard prophylactic treatment in patients with metabolic disorder.

[Summary]
Renal calculi were detected in 21% of male and 13% of female patients with ADPKD. Anatomical urinary retention and metabolic disturbance in patients with ADPKD tend to cause development of renal stones. The main component of the stones is uric acid, and the most common metabolic abnormality is hyperoxaluria. Medical preventive treatments are not recommended because of the lack of studies that prove their efficacy. General preventive measures are recommended for fluid intake and diet.

CQ 11. Is transthoracic echocardiography (TTE) for screening of valvular disease recommended to improve the mortality of ADPKD patients?

Recommendation Grade: C1
We suggest a TTE study for valvular disease only if the patients have heart murmur to evaluate the severity of valvular diseases.

[Summary]
Mitral valve prolapse and mitral regurgitation (MR) are the common cardiac complications in ADPKD. Twenty-one percent of Japanese ADPKD patients have MR. However, solid data on the natural history of valvular disease in ADPKD are currently lacking, and studies with long-term follow-up periods are also very few.
According to the reports regarding non-ADPKD patients, mild or trivial MR carries better prognosis and is thought not to affect the loss of cardiac function and mortality in cardiovascular diseases.
For patients with a heart murmur, it is uncertain whether the disease is mild or severe. TTE might be useful to evaluate indications for surgical treatments and improve the mortality of these ADPKD patients.

CQ 12. Should ADPKD patients with ESRD undergo renal transarterial embolization to reduce enlarged kidneys?

Recommendation Grade: C1
Renal transarterial embolization in ADPKD patients with ESRD is effective in reducing the size of enlarged kidneys and is therefore recommended.

[Summary]
As ADPKD patients age, kidney enlargement becomes increasingly pronounced, with some patients experiencing considerable abdominal bloating. Such patients are unable to eat properly, leading to malnutrition and an overall deterioration of health. However, there is no clear treatment for massively enlarged kidneys. The literature remains sparse on renal transarterial embolization in ADPKD patients with enlarged kidneys, and reports differ as to the embolism type. However, as renal transarterial embolization was demonstrated to reduce kidney swelling in all existing reports, the procedure is believed to be effective for ADPKD patients and is therefore recommended despite the paucity of evidence.

CQ 13. Should ADPKD patients with ESRD undergo hepatic transarterial embolization to reduce hepatomegaly?

Recommended Grade: C1
Hepatic transarterial embolization in ADPKD patients with ESRD is effective in reducing hepatomegaly and is therefore recommended.

[Summary]
As ADPKD patients age, liver cysts proliferate and hepatomegaly becomes increasingly pronounced, with some patients experiencing extreme abdominal bloating. Such patients are unable to eat properly, leading to malnutrition and an overall deterioration of health. However, there is no clear treatment for a massively enlarged liver. There are limited reports of hepatic transarterial embolization in ADPKD patients with hepatomegaly, but they are individual or collected case reports, as opposed to scientific studies. The evidence presented in these reports is meager, but as there is some suggestion that hepatic transarterial embolization may be effective in ADPKD patients